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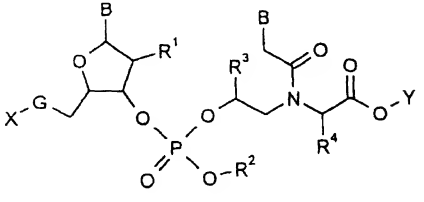
(54) **BLOCS POUR CO-OLIGOMERES DNA/PNA**
(54) **BUILDING BLOCKS FOR DNA/PNA CO-OLIGOMERS**



(I),

(57) L'invention porte sur des composés de formule générale (I) (voir formule I), où les substituants ont le sens donné dans la description. Ces composés conviennent pour la préparation de co-oligomères PNA/DNA strictement alternés, jusqu'ici inconnus.

(57) The invention relates to compounds of the general formula (I) (see formula I) in which the substituents have the meanings indicated in the description. The compounds are suitable for the preparation of hitherto unknown strictly alternating PNA/DNA co-oligomers.

**Building blocks for DNA/PNA co-oligomers**

Peptide nucleic acids (PNA) are polyamide compounds which carry purines or pyrimidines in the side chain. They are thus formally compounds which are analogous to DNA, in which the deoxyribose phosphate structure has been replaced by a polyamide backbone.

The deliberate switching off of gene expression by complementary nucleic acids, so-called antisense oligonucleotides, is a new therapeutic approach. Possible applications extend from the treatment of viral infections to the therapy of cancer (S. Agrawal, Tibtech 10, 152 (1992); W. James, Antiviral Chemistry & Chemotherapy 2, 191 (1991); B. Calabretta, Cancer Research 51, 4504 (1991)). The control of gene expression takes place at the level of DNA and RNA and is already possible with unmodified oligonucleotides (C. Helene, Anti-Cancer Drug Design 6, 569 (1991); E. Uhlmann, A. Peymann, Chemical Reviews 90, 543 (1990)). However, these are unsuitable for therapeutic applications on accounts of lack of enzymatic stability and excessively low absorption in cellular systems. Therapeutic applications require chemically modified antisense oligonucleotides.

Besides the antisense strategy, an inhibition of gene expression can also be achieved by the sense strategy. In this, the sense oligonucleotides compete specifically with DNA binding proteins such as, for example, transcription factors (M. Blumengeld, Nucleic Acids Research 21, 3405 (1993)).

Oligonucleotides having a modified internucleotide phosphate or a phosphate-free internucleotide linkage have been systematically investigated in many studies; their synthesis, however, proved to be very complicated and the therapeutic effects observed to be inadequate (E. Uhlmann, A. Peyman, Chemical Reviews 90, 543 (1990)).

An alternative for the modification or substitution of the phosphate group in nucleic acids is the complete replacement of ribose and phosphate by other backbones. This concept was realized for the first time by Pitha et al., who replaced ribose phosphate by poly-N-vinyl derivatives, which leads to so-called "plastic DNA" (J. Pitha, P.O.P. Ts'O, J. Org. Chem. 33, 1341 (1968); J. Pitha, J. Adv. Polym. Sci. 50, 1 (1983)). However, it does not allow the deliberate synthesis of defined sequences.

The synthesis of defined sequences is possible if, instead of sugar phosphate, for example, a polyamide backbone is used which, in analogy to the conventional peptide synthesis (M. Bodanszky, Principles of Peptide Synthesis, Springer, Berlin 1984) is synthesized stepwise. This concept was realized in different ways by various teams (J.E. Summerton et al. WO 86/05518; R.S. Varma et al. WO 92/18518; O. Buchardt et al. WO 92/20702; H. Wang, D.D. Weller, Tetrahedron Letters 32, 7385 (1991); P. Garner, J.U. Yoo, Tetrahedron Letters 34, 1275 (1993); S.-B. Huang, J.S. Nelson D.D. Weller, J. Org. Chem. 56, 6007 (1991); Bayer AG EP 646 595 A1, EP 646 596 A1 and EP 700 928 A1; Hoechst AG EP 672 661 A1, EP 672 677 A2, EP 672 700 A1).

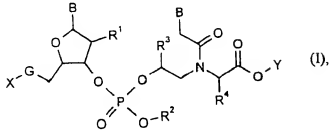
Polyamide nucleic acids are also suitable for diagnostic and molecular biology applications (Buchardt et al. WO 92/20703 and Glaxo Inc. WO 93/12129).

Since oligomers from pure PNA units have proved to be too lipophilic and thus incapable of cell wall penetration, it was possible to reduce this problem by means of combinations of "hydroxy-substituted" PNA monomers with 5'-amino-2',5'-dideoxynucleotides or 2'-deoxynucleotides to give DNA/PNA co-oligomers (cf. Hoechst AG EP 672 677 A2). Hetero-oligomeric compounds having a backbone of 2-aminoethyl-glycine and L-trans-aminoproline have proved to be superior with respect to binding strength for the complementary DNA compared with compounds having a pure 2-aminoethylglycine backbone (cf. EP 700 928 A1). It is the intention of the present invention, by replacement of the 2-aminoethylglycine by nucleotide derivatives and of the aminoproline by 2-hydroxyethylglycine analogues, to arrive at compounds with stronger binding to the complementary DNA with simultaneous increase in hydrophilicity.

The co-oligomers are suitable for the control of gene expression. Furthermore, substances of this type can be used in diagnostics and molecular biology for the isolation, identification and quantification of nucleic acids.

During work on structures of this type the synthesis of new hydroxyethylglycine and 3'-linked nucleotide-hydroxyethylglycine units was possible. The latter are suitable for the preparation of hitherto unknown strictly alternating PNA/DNA co-oligomers.

The invention relates to compounds of the general formula (I)



(I),

in which

$R^1$ represents hydrogen, hydroxyl, $C_1$-$C_{18}$-alkoxy, halogen, azido or amino,

$R^2$ represents a phosphate protective group customary in nucleotide chemistry, such as, for example, 2-cyanoethyl,

$R^3$ and $R^4$ independently of one another represent hydrogen, $C_1$-$C_4$-alkyl or together represent $C_1$-$C_4$-alkanediyl such as, for example, $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$ or $-C(CH_3)_2-$,

B represents all natural or unnatural nucleobases, such as, for example, thymine, uracil, cytosine, adenine, guanine, hypoxanthine or derivatives derived by chemical modification of these or halogenated precursors of these, optionally substituted on the amino groups by protective groups such as acetyl, trifluoroacetyl, trichloroacetyl, benzoyl, phenylacetyl, benzyloxycarbonyl (Z or Cbz), tert-butoxycarbonyl (Boc), allyloxycarbonyl, (9-fluorenyl)methoxycarbonyl (Fmoc) or other protective groups customary in peptide and nucleic acid chemistry,

G represents -NH- or -O-,

X represents hydrogen or any desired protective group known from peptide chemistry, such as, for example, Z, Fmoc or 4-methoxytrityl and

Y represents hydrogen, $C_1$-$C_6$-alkyl or any desired C-terminal protective group known from peptide chemistry, such as, for example, benzyl or tert-butyl.

The compounds of the formula (I) according to the invention are suitable as DNA/PNA building blocks (or units) for the preparation of DNA/PNA co-oligomers, for example according to standard processes, in particular of peptide chemistry, for esterifications and amidations in the solid and liquid phase (cf. EP 700 928 A1, p. 5 and other refs. cited there).

Formula (I) provides a general definition of the DNA/PNA building blocks according to the invention.

$R^1$ preferably represents hydrogen, hydroxyl, $C_1$-$C_6$-alkoxy, fluorine, chlorine, bromine, azido or amino.

$R^2$ preferably represents a phosphate protective group customary in nucleotide chemistry, such as, for example, 2-cyanoethyl.

$R^3$ and $R^4$ preferably independently of one another represent hydrogen, $C_1$-$C_4$-alkyl or together represent $C_1$-$C_4$-alkanediyl such as, for example, $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$ or $-C(CH_3)_2-$.

B preferably represents all natural nucleobases, such as, for example, thymine, uracil, cytosine, adenine, guanine or hypoxanthine or halogenated precursors of these which are optionally substituted on the amino groups by protective groups such as acetyl, trifluoroacetyl, trichloroacetyl, benzoyl, phenylacetyl, benzyloxycarbonyl, tert-butoxycarbonyl, allyloxycarbonyl, (9-fluorinyl)methoxycarbonyl or other protective groups customary in peptide and nucleic acid chemistry.

G preferably represents -NH- or -O-.

X preferably represents hydrogen or any desired protective group known from peptide chemistry, such as, for example, Z, Fmoc or 4-methoxytrityl.

Y preferably represents hydrogen, $C_1$-$C_4$-alkyl or any desired C-terminal protective group known from peptide chemistry, such as, for example, benzyl or tert-butyl.

$R^1$ particularly preferably represents hydrogen, hydroxyl, methoxy, ethoxy, fluorine, chlorine, azido or amino.

$R^2$ particularly preferably represents 2-cyanoethyl.

$R^3$ and $R^4$ particularly preferably independently of one another represent hydrogen, methyl, ethyl, isopropyl or together represent $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$ or $-C(CH_3)_2-$.

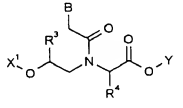
B particularly preferably represents all natural nucleobases, such as, for example, thymine, uracil, cytosine, adenine, guanine or hypoxanthine or halogenated precursors of these which are optionally substituted on the amino groups by protective groups such as acetyl, trifluoroacetyl, trichloroacetyl, benzoyl, phenylacetyl, benzyloxycarbonyl, tert-butoxycarbonyl, allyloxycarbonyl, (9-fluorenyl)methoxycarbonyl or other protective groups customary in peptide and nucleic acid chemistry.

G particularly preferably represents -NH- or -OH-.

X particularly preferably represents hydrogen or any desired protective group known from peptide chemistry, such as, for example, Z, Fmoc or 4-methoxytrityl.

Y particularly preferably represents hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl or any desired C-terminal protective group known from peptide chemistry, such as, for example, benzyl or tert-butyl.

The invention furthermore relates to compounds of the general formula (II)



(II),

in which

$R^3$, $R^4$ and B have the meanings indicated in the description of the compounds of the formula (I),

$X^1$ represents hydrogen or an acid-labile protective group known from peptide chemistry, such as, for example, silyl substituted by alkyl and/or phenyl, Z, Fmoc or 4-methoxytrityl, where in the case in which $R^3$ and $R^4$ simultaneously each represent hydrogen, optionally substituted alkoxycarbonyl and trityl are excluded and

Y represents $C_1$-$C_6$-alkyl or any desired C-terminal protective group known from peptide chemistry, such as, for example, benzyl or tert-butyl.

Formula (II) provides a general definition of the PNA building blocks according to the invention.

$R^3$, $R^4$ and B preferably represent the radicals indicated as preferred in the description of the compounds of the formula (I).

$X^1$ preferably represents hydrogen or an acid-labile protective group known from peptide chemistry such as, for example, silyl substituted by alkyl and/or phenyl (e.g. tert-butyldimethylsilyl or tert-butyldiphenylsilyl), Z, Fmoc or 4-methoxytrityl, where in the case in which $R^3$ and $R^4$ simultaneously each represent hydrogen, optionally substituted alkoxycarbonyl and trityl are excluded.

Y preferably represents $C_1$-$C_4$-alkyl or any desired C-terminal protective group known from peptide chemistry, such as, for example, benzyl or tert-butyl.

$R^3$, $R^4$ and B particularly preferably represent the radicals indicated as particularly preferred in the description of the compounds of the formula (I).

$X^1$ preferably represents hydrogen or silyl substituted by alkyl and/or phenyl, such as, for example, tert-butyldimethylsilyl or tert-butyldiphenylsilyl.

Y particularly preferably represents methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl or any desired C-terminal protective

group known from peptide chemistry, such as, for example, benzyl or tert-butyl.

The protective groups known from peptide chemistry are mentioned, for example, in T.W. Greene, P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd Ed., John Wiley & Sons, New York 1991.

The abovementioned definitions or explanations of radicals mentioned generally or in preferred ranges can be combined with one another in any desired manner, i.e. also between the particular ranges and preferred ranges. They apply correspondingly to the final products and to the precursors and intermediates.

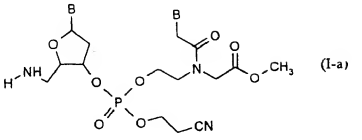
Preferred compounds of the formula (I) according to the invention are those in which a combination of the meanings mentioned as preferred (preferable) above are present.

Particularly preferred compounds of the formula (I) according to the invention are those in which a combination of the meanings mentioned as particularly preferred above are present.

Saturated or unsaturated hydrocarbon radicals such as alkyl or alkenyl, even in compounds with heteroatoms, such as, for example, in alkoxy, can, if possible, in each case be straight-chain or branched.

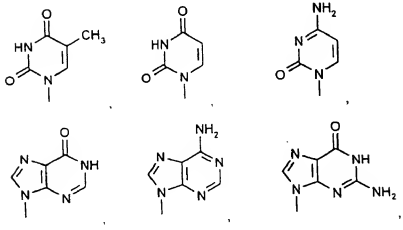
Optionally substituted radicals can be mono- or polysubstituted, it being possible in the case of polysubstitution for the substituents to be identical or different.

Examples of the compounds of the formula (I) according to the invention are units of the formula (I-a):



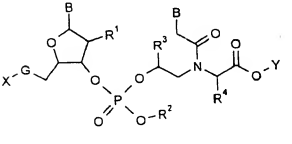
(I-a)

B =



, etc.

A) DNA/PNA building blocks of the formula (I)

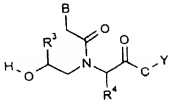


(I).

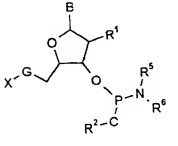
in which

$R^1$ to $R^4$, B, G, X and Y have the meaning indicated above,

can be prepared by reacting compounds of the formula (II-a)


(II-a),

with nucleotide derivatives of the formula (III)


(III),

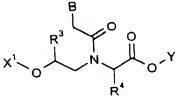
in which

$R^1$, $R^2$, B, G and X have the meaning indicated above and

$R^5$ and $R^6$ independently of one another in each case represent $C_1$-$C_4$-alkyl,

in the presence of a diluent and of a reaction auxiliary and then oxidizing the products.

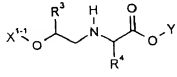
B) PNA building blocks of the formula (II)


(II),

in which

$R^3$, $R^4$, B, $X^1$ and Y have the meaning indicated above

can be prepared by reacting protected hydroxyethylglycine derivatives of the formula (IV)



(IV),

in which

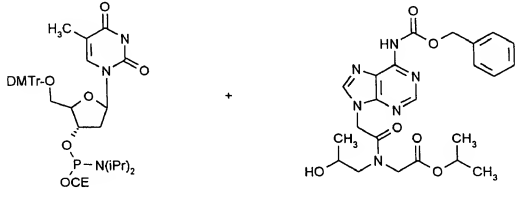
$X^{1-1}$ with the exception of hydrogen has the same meaning as $X^1$,

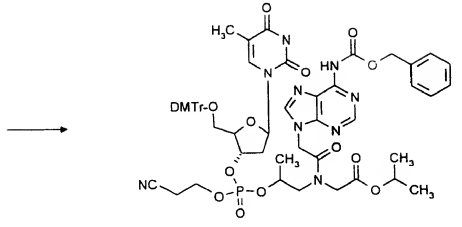
with acetic acids substituted by nucleobases, of the formula (V)

$$B\text{-}CH_2\text{-}COOH \qquad (V)$$

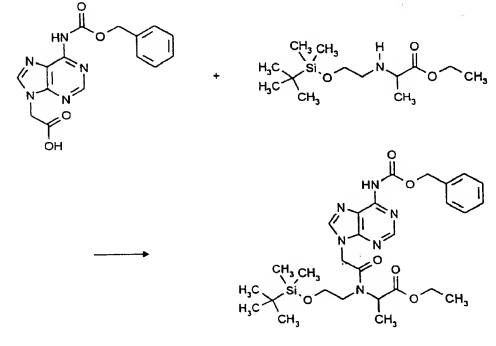
in the presence of a reaction auxiliary and of a diluent and, if appropriate, in the presence of a base and in the case in which $X^1$ should be H [formula (II-a)], then removing the protective group using a suitable reagent.

If, for example, N-(2-hydroxy-2-methyl-ethyl)-N-[($N^6$-benzyloxycarbonyl-adenin-1-yl)-acetyl]-glycine isopropyl ester and 2-cyanoethyl N,N-diisopropyl-5'-O-(dimethoxy-trityl)-thymidine-3'-phosphoramidite are used as starting substances, the course of the reaction of process (A) according to the invention can be shown by the following scheme:





If, for example, ($N^6$-benzyloxycarbonyl-adenine-1-yl)-acetic acid and [N-(2-dimethyl-$^t$butylsilyloxy)-ethyl]-alanine ethyl ester are used as starting substances, the course of reaction of process (B) according to the invention can be shown by the following scheme:



The PNA building blocks of the formula (II-a) needed for carrying out process (A) according to the invention are a subset of the new compounds of the formula (II) in which $X^1$ represents hydrogen. They can be prepared, for example, by process (B).

Formula (III) provides a general definition of the nucleotide derivatives furthermore needed for carrying out process (A) according to the invention. In this formula, $R^1$, $R^2$, G and X preferably represent those radicals which have already been mentioned as preferred in the description of the units of the formula (I). $R^5$ and $R^6$ preferably in each case represent methyl, ethyl, n-, sec- or iso-propyl.

The compounds of the formula (III) are known or can be prepared by known methods (cf. M.J. Gait (ed.) Oligonucleotide Synthesis, A Practical Approach, IRL Press, Oxford 1984).

Formula (IV) provides a general definition of the hydroxyethylglycine derivatives needed for carrying out process (B) according to the invention. In this formula, $R^3$, $R^4$ and Y preferably represent those radicals which have already been mentioned as preferred in the description of the units of the formula (I). $X^{1-1}$ preferably represents, excluding hydrogen, the same radicals which preferably represent $X^1$ in formula (II).

Compounds of the formula (IV) can be prepared, for example, by removing the protective group $X^2$ from completely protected hydroxyethylglycine derivatives of the formula (VI) according to the following reaction scheme:

(VI) (IV)

In the formula (VI), $X^2$ represents an N-terminal protective group which is suitable depending on Y, such as, for example, tert-butoxycarbonyl (**BOC**), benzyloxycarbonyl (Cbz) or benzyl (Bzl), preferably Bzl or Cbz (cf., for example, T.W. Greene, P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd Ed., John Wiley & Sons, New York 1991).

The reaction can be carried out by means of customary methods of N-terminal deblocking such as acidolysis, for example in the case of the BOC group, or catalytic hydrogenation, for example in the case of a benzyl ester.

Compounds of the formula (VI) can be prepared, for example, by protecting the hydroxy group of the hydroxyethylglycine derivatives of the formula (VII) according to customary methods as in the following reaction scheme (cf. the abovementioned literature):

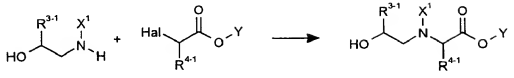
(VII) (VI)

Compounds of the formula (VII) can be prepared, for example, by esterifying or protecting the carboxyl group of the hydroxyethylglycine derivatives of the formula (VIII) according to customary methods as in the following reaction scheme:

(VIII) (VII)

Hydroxyethylglycine derivatives of the formula (VIII) are in some cases commercially available, are known or can be prepared by known methods.

Specific compounds (VII-a) of the formula (VII) can also be prepared, for example, by reacting N-protected hydroxyethanols of the formula (IX) with α-bromocarboxylic acid derivatives of the formula (X) according to customary methods as in the following reaction scheme:



(IX) (X) (VII-a)

In the formulae (VII-a), (IX) and (X), $R^{3-1}$ and $R^{4-1}$ independently of one another represent hydrogen or $C_1$-$C_4$-alkyl.

Compounds of the formula (IX) and (X) are commercially available, generally known or can be prepared according to known methods (cf. Burfield et al., J. Chem. Soc. Perkin Trans. I, **1977**, 666).

The substituted acetic acids of the formula (V) furthermore needed for carrying out process (B) according to the invention are known or can be prepared by known methods (cf. Dueholm et al. J. Org. Chem. **59**, 5767 (1994)).

Process (A) according to the invention is preferably carried out in solution, but can also be carried out in the solid phase (see: R.B. Merrifield, J. Am. Chem. Soc. **85**, 2149 (1963) and M.J. Gait, (ed.) Oligonucleotide Synthesis, A Practical Approach, IRL Press, Oxford 1984).

Suitable reaction auxiliaries for carrying out the phosphotriester formation of process (A) according to the invention are all activators which are suitable for the formation of a phosphite bond and all oxidizing agents which are suitable for the conversion of the phosphite into the corresponding phosphate (Shabarova, Z.; Bogdanov, A., Advanced Organic Chemistry of Nucleic Acids, Verlag Chemie, Weinheim 1994). The following activators are preferably suitable: azoles such as tetrazoles, triazoles and their ammonium salts. Suitable oxidizing agents are preferably: peracids such as 3-chloroperbenzoic acid, solutions of iodine in solvent mixtures of water, THF, tert-amines.

Possible diluents for carrying out process (A) according to the invention are organic solvents and any desired mixtures thereof. Examples which may be mentioned are: aliphatic, alicyclic or aromatic hydrocarbons, such as, for example, petroleum ether, hexane, heptane, cyclohexane, methylcyclohexane, benzene, toluene, xylene or decalin; halogenated hydrocarbons, such as, for example,

toluene, xylene or decalin; halogenated hydrocarbons, such as, for example, chlorobenzene, dichlorobenzene, methylene chloride, chloroform, tetrachloromethane, dichloroethane, trichloroethane or tetrachloroethylene; ethers, such as diethyl ether, diisopropyl ether, methyl t-butyl ether, methyl t-amyl ether, dioxane, tetrahydrofuran, 1,2-dimethoxyethane, 1,2-diethoxyethane, diethylene glycol dimethyl ether or anisole; ketones, such as acetone, butanone, methyl isobutyl ketone or cyclohexanone; nitriles, such as acetonitrile, propionitrile, n- or i-butyronitrile or benzonitrile; amides, such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylformanilide, N-methylpyrrolidone or hexamethyl-phosphoramide; N-oxides such as N-methylmorpholine-N-oxide; esters such as methyl acetates, ethyl acetates or butyl acetates; sulfoxides, such as dimethyl sulfoxide; sulfones, such as sulfolane.

The reaction temperature in process (A) according to the invention can be varied within a wide range. In general, the condensation is carried out at temperatures between -30°C and +80°C, preferably at -10°C to 60°C, particularly preferably at 0°C to room temperature.

When carrying out process (A) according to the invention, 0.5 to 3 mol, preferably 0.8 to 1.5 mol, of compound of the formula (II) and 1 to 3 mol of the reaction auxiliary and the oxidizing agent, in general in the molar ratio from 1:1 to 1:4, preferably 1:2 to 1:3, are employed per mole of compound of the formula (III).

Suitable reaction auxiliaries for carrying out the amidation of process (B) according to the invention are all compounds which are suitable for the coupling of an amide bond (cf., for example, Houben-Weyl, Methoden der Organischen Chemie [Methods of Organic Chemistry], Volume 15/2; Bodanszky et al., Peptide Synthesis 2nd ed., Wiley & Sons, New York 1976). The following methods are preferably suitable: the active ester method using pentafluorophenol (PfP), N-hydroxysuccinimide, 1-hydroxybenzotriazole (HOBt), coupling with carbodiimides such as dicyclohexylcarbodiimide or N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide (EDC or EDCI) and also the mixed anhydride method or coupling with phosphonium reagents such as 1-benzotriazolyloxy-tris-(dimethylaminophosphonium) hexafluorophosphate (BOP), Bis-(2-oxo-3-oxazolidinyl)-phosphoryl chloride (BOP-Cl) or with phosphonic acid ester reagents such as diethyl cyanophosphonate (DEPC) and diphenylphosphoryl azide (DPPA). Coupling with BOP-Cl or EDCI in the presence of HOBt is particularly preferred.

Suitable diluents for carrying out process (B) according to the invention are organic solvents and any desired mixtures thereof. Examples which may be mentioned are: aliphatic, alicyclic or aromatic hydrocarbons, such as, for example, petroleum ether, hexane, heptane, cyclohexane, methylcyclohexane, benzene, toluene, xylene or decalin; halogenated hydrocarbons, such as, for example, chlorobenzene, dichlorobenzene, methylene chloride, chloroform, tetrachloromethane, dichloroethane, trichloroethane or tetrachloroethylene; ethers, such as diethyl ether, diisopropyl ether, methyl t-butyl ether, methyl t-amyl ether, dioxane, tetrahydrofuran, 1,2-dimethoxyethane, 1,2-diethoxyethane, diethylene glycol dimethyl ether or anisole; ketones, such as acetone, butanone, methyl isobutyl ketone or cyclohexanone; nitriles, such as acetonitrile, propionitrile, n- or i-butyronitrile or benzonitrile; amides, such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylformanilide, N-methylpyrrolidone, 1,3-dimethyl-tetrahydro-2-pyrimidinone (DMPU), 1,3-dimethyl-2-imidazolidinone, tetramethylurea or hexamethylphosphoramide; N-oxides such as N-methylmorpholine-N-oxide; esters such as methyl acetate, ethyl acetate or butyl acetate; sulfoxides, such as dimethyl sulfoxide; sulfones, such as sulfolane.

The amidation is preferably carried out in the presence of a base. Those suitable are inorganic or organic bases. These preferably include alkaline earth metal or alkali metal hydroxides, alkoxides, acetates, carbonates or hydrogencarbonates, such as, for example, sodium, potassium or ammonium hydroxide, sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium, potassium, calcium or ammonium acetate, sodium, potassium or ammonium carbonate, sodium hydrogencarbonate or potassium hydrogencarbonate, and tertiary amines, such as trimethylamine, triethylamine, tributylamine, ethyl-diisopropylamine, N,N-dimethylaniline, N,N-dimethyl-benzylamine, pyridine, picoline, N-methyl-piperidine, N-methylmorpholine, N,N-dimethylaminopyridine, diazabicyclooctane (DABCO), diazabicyclononene (DBN) or diazabicycloundecene (DBU).

The reaction temperature can be varied within a relatively wide range in process (B) according to the invention. In general, the condensation is carried out at temperatures between -80°C and +150°C, preferably at -50°C to 100°C, particularly preferably at -30°C to room temperature.

When carrying out process (B) according to the invention, 1 to 5 mol, preferably 1.5 to 3 mol, of acetic acid of the formula (V) and 1 to 3 mol of reaction auxiliary

and the base, in general in a molar ratio of 1:1 to 1:3, preferably 1:1.5 to 1:2.5, are employed per mole of compound of the formula (IV).

The protective group can be removed by known methods (cf., for example, T.W. Greene, P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd Ed., John Wiley & Sons, New York 1991).

The reactions of the processes according to the invention can be carried out at normal pressure or at elevated pressure, preferably they are carried out at normal pressure. Working up is carried out by customary methods of organic chemistry. The final products are preferably purified by crystallization, chromatographic purification or by removal of the volatile constituents, if appropriate in vacuo.

**Experimental Section**

**Example 1: N-Benzyloxycarbonyl-4-hydroxy-L-trans-proline methyl ester**

25.1 g of N-benzyloxycarbonyl-4-hydroxy-L-trans-proline are dissolved in 450 ml of anhydrous methanol and adjusted to pH = 9.0-9.5 using caesium carbonate. After stirring at room temperature for 30 minutes, the mixture is evaporated to dryness and the residue is dried overnight in a high vacuum. The residue is taken up in N,N-dimethylformamide (DMF), 14.8 g of methyl iodide are slowly added dropwise to the suspension such that the temperature of the reaction mixture does not exceed 30°C and it is stirred for a further 12 hours. The solvent is removed, and the residue which remains is coevaporated several times with toluene and taken up in dichloromethane. The solution is washed with water/satd sodium chloride solution 1:1 (v/v), 5% strength $NaHCO_3$ soln and water/sodium chloride solution again. The organic phase is dried over $MgSO_4$ and concentrated, and the resulting oil is dried in a high vacuum.

Yield: 21.86 g

$R_f$: 0.15 Eluent: toluene/ethanol 10:1

**Example 2: N-Z-4-($^t$Butyldimethylsilyloxy)-L-trans-pr line methyl ester**

14.4 g (51.7 mmol) of N-Z-4-hydroxy-L-trans-proline methyl ester are dissolved in 150 ml of N,N-dimethylformamide under argon and treated with 14.8 ml of triethylamine. 10.4 g (68.8 mmol) of $^t$butyldimethylsilyl chloride (TBDMSi chloride) are added dropwise in the course of 10 minutes and the mixture is stirred overnight. After removing the solvent in vacuo, an oil remains which is partitioned between dichloromethane and water. The aqueous phase is extracted several times more with dichloromethane, dried over sodium sulphate and the solvent is evaporated in vacuo. The residue is then purified by chromatography on silica gel using dichloromethane/methanol (60:1, v/v) as eluent.

Yield: 13.95 g
$R_f$: 0.54 Eluent: $CH_2Cl_2$/MeOH 40:1

**Example 3: 4-($^t$Butyldimethylsilyloxy)-L-trans-proline methyl ester**

The compound from Example 2 (3.8 g; 9.6 mmol) is dissolved in anhydrous methanol (40 ml) and hydrogenated for 4 hours over palladium/activated carbon (10%; 0.3 g) at normal pressure and room temperature. After complete reaction, the catalyst is filtered off and the filtrate is concentrated in vacuo.

Yield: 2.4 g
$R_f$: 0.52 Eluent: $CH_2Cl_2$/MeOH 10:1

**Example 4: 4-($^t$Butyldimethylsilyloxy)-N-[(thymin-1-yl)-acetyl]-L-trans-proline methyl ester**

3.4 g (18.5 mmol) of 1-carboxymethyl-thymine are dissolved in 50 ml of DMF, cooled to -30°C and treated at this temperature with 1.3 eq. of HOBt.$H_2O$ and 1.3 eq. of EDCI.HCl. The mixture is stirred at -30°C for 30 min and a solution of 2.4 g (19.3 mmol) of 4-($^t$butyldimethylsilyloxy)-L-trans-proline methyl ester in DMF and 4.5 ml of triethylamine are added. The mixture is stirred at -30°C for 1 hour and then additionally stirred overnight at room temperature. It is then concentrated, the residue is taken up in ethyl acetate and the solution is washed in

each case with 1 N HCl, saturated sodium hydrogen carbonate solution and saturated NaCl solution. The product crystallizes out of the organic phase overnight, is filtered off and dried in a high vacuum.

Yield: 3.03 g
$R_f$: 0.68 Eluent: $CH_2Cl_2$/MeOH 9:1

**Example 5: 4-Hydroxy-N-[(thymin-1-yl)-acetyl]-L-trans-proline methyl ester**

2.0 g of 4-($^t$butyldimethylsilyloxy)-N-[(thymin-1-yl)-acetyl]-L-trans-proline methyl ester are dissolved in 50 ml of methanol, treated with 5 drops of concentrated hydrochloric acid and stirred overnight at room temperature. The solution is completely evaporated in a high vacuum and the residue is purified by chromatography on silica gel using dichloromethane/methanol (60:1, v/v) as eluent.

Yield: 1.19 g
$R_f$: 0.21 Eluent: $CH_2Cl_2$/MeOH 20:1

**Example 6: N-Benzyl-N-(2-hydroxyethyl)-glycine $^t$butyl ester**

A solution of 9.6 g (63.4 mmol) of N-benzylethanolamine and 8.85 ml of triethylamine in 65 ml of N,N-dimethylformamide is treated at 0°C with 1 eq. of $^t$butyl bromoacetate and additionally stirred at room temperature for 22 h. After concentration, the residue is codistilled several times with toluene, taken up in dichloromethane and extracted several times with water. The organic phase is evaporated to dryness, and the residual oil is dried in a high vacuum.

Yield: 14.5 g
$R_f$: 0.47 Eluent: EA (ethyl acetate)

**Example 7: N-Benzyl-N-(2-hydroxyethyl)-glycine methyl ester**

The reaction of 41.9 g (277 mmol) of N-benzylethanolamine with methyl bromoacetate analogous to Example 6 yields N-benzyl-N-(2-hydroxyethyl)-glycine methyl ester.

Yield: 43.8 g

$R_f$: 0.53 Eluent: $CH_2Cl_2$/MeOH 20:1

**Example 8: N-Benzyl-N-(2-hydroxyethyl)-glycine methyl ester**

The reaction of 34.4 g (277 mmol) of N-benzylethanolamine with ethyl bromoacetate analogous to Example 6 yields N-benzyl-N-(2-hydroxyethyl)-glycine ethyl ester.

Yield: 43.9 g

$R_f$: 0.49 Eluent: $CH_2Cl_2$/MeOH 20:1

**Example 9: N-Benzyl-N-(2-$^t$butyldiphenylsilyloxyethyl)-glycine $^t$butyl ester**

5.2 g (19.5 mmol) of N-benzyl-N-(2-hydroxyethyl)-glycine $^t$butyl ester are dissolved in 50 ml of DMF under argon and treated with 5.5 ml of triethylamine. A solution of 1.3 eq. of TBDPSi chloride is added dropwise and the mixture is additionally stirred overnight. The solvent is removed and the residue is partitioned between water and dichloromethane. The aqueous phase is extracted a further three times with dichloromethane and the combined organic phases are then dried over sodium sulphate. The crude product is purified by chromatography on silica gel using ethylacetate/hexane (1:9, v/v) as eluent.

Yield: 6.79 g

$R_f$: 0.68 Eluent: EA/hexane 1:9

**Example 10: N-Benzyl-N-(2-$^t$butyldimethylsilyloxy-ethyl)-glycine methyl ester**

The reaction of 37.7 g (170 mmol) of N-benzyl-N-(2-hydroxyethyl)-glycine methyl ester with $^t$butyldimethylsilyl chloride analogous to Example 9 yields N-benzyl-N-(2-$^t$butyldimethylsilyloxy-ethyl)-glycine methyl ester as an oil after high-vacuum drying.

Yield: 45.1 g
$R_f$: 0.39 Eluent: EA/hexane 1:9

**Example 11: N-Benzyl-N-(2-$^t$butyldimethylsilyloxyethyl)-glycine ethyl ester**

30.1 g (127 mmol) of N-benzyl-N-(2-$^t$butyldimethyl-silyloxyethyl)-glycine ethyl ester are reacted with 1.3 eq. of TBDMSi chloride under the conditions of Example 10.

Yield: 27.3 g
$R_f$: 0.49 Eluent: EA/hexane 1:10

**Example 12: N-(2-$^t$butyldiphenylsilyloxyethyl)-glycine $^t$butyl ester**

To remove the benzyl protective group, 5.9 g (11.7 mmol) of N-benzyl-N-(2-$^t$butyldiphenylsilyloxy-ethyl)-glycine $^t$butyl ester are dissolved in 50 ml of anhydrous methanol and hydrogenated for 36 hours over palladium/activated carbon (10%; 0.5 g) at room temperature and normal pressure. After complete reaction (TLC checking), the catalyst is filtered off and the filtrate is evaporated in vacuo.

Yield: 4.91 g
$R_f$: 0.46 Eluent: EA/PE (petroleum ether) 1:9

**Example 13: N-(2-$^t$butyldimethylsilyloxy-ethyl)-glycine methyl ester**

The analogous hydrogenation of 23.8 g (71 mmol) of the compound from Example 10 yields N-(2-$^t$butyldimethylsilyloxy-ethyl)-glycine methyl ester.

Yield: 16.7 g
$R_f$: 0.24 Eluent: EA/PE 1:1

**Example 14: N-(2-$^t$butyldimethyl-silyloxyethyl)-glycine ethyl ester**

The reaction of 20.0 g (57.0 mmol) of N-benzyl-N-(2-$^t$butyldimethylsilyloxyethyl)-glycine ethyl ester analogous to Example 13 yields the desired glycine ethyl ester as an oil.

Yield: 13.5 g
$R_f$: 0.61 Eluent: $CH_2Cl_2$/MeOH 20:1

**Example 15: N-(2-$^t$butyldiphenylsilyloxy-ethyl)-N-(thymin-1-yl-acetyl)-glycine $^t$butyl ester**

4.4 g (23.6 mmol) of 1-carboxymethyl-thymine are dissolved in 50 ml of DMF, and the solution is cooled to -30°C and treated at this temperature with HOBt x $H_2O$ and EDCI x HCl (in each case 1.3 eq.). After 30 min, a solution of 4.9 g (11.8 mmol) of the compound from Example 12 and 6 ml of triethylamine are added at this temperature. The mixture is stirred at -30°C for a further hour and then at room temperature for 12 h. It is then concentrated, the residue is taken up in ethyl acetate and the solution is washed in each case with 1 N HCl, satd $NaHCO_3$ soln. and satd NaCl soln. The crude product is purified by chromatography on silica gel using dichloromethane/methanol (10:1, v/v) as eluent and obtained after drying as a white foam.

Yield: 3.3 g
$R_f$: 0.73 Eluent: $CH_2Cl_2$/MeOH 9:1

**Example 16: N-(2-$^t$butyldimethylsilyloxy-ethyl)-N-(thymin-1-yl-acetyl)-glycine methyl ester**

The reaction comparable to Example 15 with 10.0 g (40.4 mmol) of the substance from Example 13 yields N-(2-$^t$butyldimethylsilyloxyethyl)-N-(thymin-1-yl-acetyl)-glycine methyl ester as a white solid.

Yield: 3.55 g
$R_f$: 0.60 Eluent: $CH_2Cl_2$/MeOH 10:1

**Example 17: N-(2-$^t$butyldimethylsilyloxy-ethyl)-N-(thymin-1-yl-acetyl)-glycine ethyl ester**

In a reaction analogous to Example 16, 3.55 g (13.6 mmol) of the compound from Example 14 are employed.

Yield: 3.13 g
$R_f$: 0.63 Eluent: $CH_2Cl_2$/MeOH 5:1

**Example 18: N-(2-$^t$butyldimethylsilyloxy-ethyl)-N-[($N^4$-Z-cytosin-1-yl)-acetyl]-glycine ethyl ester**

The reaction comparable to Example 15 of 0.86 g (3.3 mmol) of N-(2-$^t$butyl-dimethylsilyloxy-ethyl)-glycine ethyl ester with 2.0 g (6.6 mmol) of ($N^4$-Z-cytosin-1-yl)-acetic acid yields N-(2-$^t$butyldimethylsilyloxy-ethyl)-N-[($N^4$-Z-cytosin-1-yl)-acetyl]-glycine ethyl ester as a white solid.

Yield: 1.08 g
$R_f$: 0.61 Eluent: $CH_2Cl_2$/MeOH 20:1

**Example 19: N-(2-hydroxyethyl)-N-(thymin-1-yl-acetyl)-glycine $^t$butyl ester**

The silyl-protected compound from Example 15 (3.2 g; 5.5 mmol) is dissolved in 20 ml of THF at 0°C and treated with 3 eq. of tetrabutylammonium fluoride

(TBAF) in the form of a 1.1 m solution in THF. The mixture is allowed to come to room temperature and is additionally stirred for a further 3 hours (TLC checking). The solvent is removed, and the residue is taken up in ethyl acetate and washed with satd $NaHCO_3$ soln and satd NaCl solution. After drying over sodium sulphate, the crude product is purified by chromatography on silica gel using dichloromethane/methanol (9:1, v/v) as eluent.

Yield: 1.10 g
$R_f$: 0.41 Eluent: $CH_2Cl_2$/MeOH 10:1

**Example 20: N-(2-hydroxyethyl)-N-(thymin-1-yl-acetyl)-glycine methyl ester**

4.0 g (9.7 mmol) of the silyl-protected alcohol from Example 16 are suspended in 30 ml of methanol and brought to pH = 1 using conc. HCl. After 3 hours, the product is filtered off, washed with methanol and dried.

Yield: 1.63 g
$R_f$ 0.38 Eluent: $CH_2Cl_2$/MeOH 10:1

**Example 21: N-(2-hydroxyethyl)-N-(thymin-1-yl-acetyl)-glycine ethyl ester**

For desilylation, 2.2 g (5.2 mmol) of the substance from Example 17 are reacted with 2-3 drops of conc. HCl in 60 ml of ethanol and the solution is additionally stirred overnight at room temperature. The reaction product is filtered off, washed and dried in a high vacuum.

Yield: 1.01 g
$R_f$ 0.29 Eluent: $CH_2Cl_2$/MeOH 20:1

**Example 22: N-(2-hydroxyethyl)-N-[($N^4$-Z-cytosin-1-yl)-acetyl]-glycine ethyl ester**

0.5 g (0.9 mmol) of the compound from Example 18 is added in portions to a solution of 0.4 g (2.7 mmol) of caesium fluoride in 20 ml of acetonitrile. The

mixture is stirred at room temperature for 24 h and then the same amount of caesium fluoride is again added. After stirring at 25°C for a further 24 h, the mixture is filtered, and the filtrate is evaporated and further purified by chromatography on silica gel using dichloromethane/methanol (80:1, v/v) as eluent.

Yield: 69 mg
$R_f$: 0.28 Eluent: $CH_2Cl_2$/MeOH 20:1

**Example 23: 5'-Azido-5'-deoxythymidine**

5.0 g (20 mmol) of thymidine dried over phosphorus pentoxide for two days in a high vacuum are stirred under argon in 100 ml of DMF and treated with 1.25 eq. of triphenylphosphine, 1.25 eq. of carbon tetrabromide and 3 eq. of lithium azide. The yellow solution is stirred overnight at room temperature. After addition of 30 ml of methanol, it is additionally stirred for a further 90 minutes and then evaporated to dryness. The crude product obtained is finally chromatographed on silica gel using dichloromethane/methanol (40:1, v/v) as eluent.

Yield: 3.72
$R_f$: 0.32 Eluent: $CH_2Cl_2$/MeOH 20:1

**Example 24: 5'-Amino-5'-deoxythymidine**

4.05 g (15.2 mmol) of 5'-azido-5'-deoxythymidine are dissolved in pyridine and stirred at room temperature for 3 hours with 1.5 eq. of triphenylphosphine. 20 eq. of water are then added and the mixture is stirred further overnight. After addition of 120 ml of water, the suspension obtained is filtered off with suction. The filtrate is washed five times with ethyl acetate and evaporated to dryness. The powder which remains is coevaporated several times with pyridine/toluene and dried in a high vacuum.

Yield: 2.78 g
$R_f$: 0.43 Eluent: $CH_2Cl_2$/MeOH 10:1

**Example 25: 5'-N-(4-methoxytrityl)-5'-amino-5'-deoxythymidine**

2.7 g (11.5 mmol) of 5'-amino-5'-deoxythymidine are initially introduced into pyridine and treated with 3 eq. of 4-methoxytrityl chloride, 1 eq. of triethylamine and a catalytic amount of DMAP. The mixture is stirred overnight with exclusion of light and then quenched with methanol. The solvent is distilled off, the residue is taken up in dichloromethane and the solution is washed with 5% strength $NaHCO_3$ soln (2x) and satd. NaCl soln. The organic phase is dried over sodium sulphate and then evaporated to dryness. The oil which remains is chromatographed on basic alumina using dichloromethane/methanol (100:0, 100:2, 100:4, 100:6, 100:8, 100:10 (v/v) in each case with 1% ammonia). The product thus obtained is dissolved in dichloromethane/triethylamine 10:1 (v/v) and precipitated by addition to 800 ml of pentane at 0°C. After 30 min at this temperature, the precipitate is filtered off and dried in a high vacuum.

Yield: 2.77 g
$R_f$: 0.46 Eluent: $CH_2Cl_2$/MeOH 10:1

**Example 26: 5'-N-(9-Fluorenylmethyloxycarbonyl)-5'-amino-5'-deoxythymidine**

3.2 g (13.3 mmol) of 5'-amino-5'-deoxythymidine are initially introduced into DMF, treated with 1.2 eq. of diisopropylethylamine and 1.2 eq. of 9-fluorenylmethyl-succinimidyl carbonate and the mixture is stirred at room temperature for 30 minutes. After reaction is complete, 175 ml of satd $NaHCO_3$ soln are added. The resulting precipitate is separated off and washed thoroughly with water. It is then dissolved in dichloromethane and chromatographed on basic alumina using dichloromethane/methanol (100:0, 100:1, 100:2, ....100:10 (v/v) in each case with 1% ammonia).

Yield: 1.56 g
$R_f$: 0.40 Eluent: $CH_2Cl_2$/MeOH 30:1

**Example 27: [N-(Ethoxycarboxymethyl)-N-(thymin-1-yl-acetyl)-2-amin ethyl]-2-cyanoethyl-5'-O-(dimethoxytrityl)-thymidine 3'-phosphate**

Both 0.2 g (0.64 mmol) of the substance from Example 21 and 0.37 g (0.5 mmol) of 2-cyanoethyl-N,N-diisopropyl-5'-O-(dimethoxytrityl)-thymidine 3'-phosphoramidite are freed from the last traces of moisture by repeated coevaporation with dichloromethane and subsequent separate high-vacuum drying for 12 h. The compound from Example 21 is dissolved in 10 ml of dichloromethane/acetonitrile (v/v) 1:1 under argon and the phosphoramidite is added followed by 37.5 mg (0.5 mol) of tetrazole, both likewise dissolved in this solvent mixture, using a syringe. After reaction is complete (TLC checking, about 5 hours), 1.2 mmol of m-CPBA are added and the mixture is additionally stirred overnight at room temperature. The reaction mixture is diluted with 150 ml of dichloromethane and treated with satd $Na_2CO_3$ solution. The aqueous phase is extracted several times more with dichloromethane, and the combined organic phases are washed with $NaHSO_3$ solution and finally dried over sodium sulphate. The solvent is removed in vacuo and the residue is purified by chromatography on silica gel (eluent dichloromethane/methanol 70:1 to 50:1 (v/v)).

Yield: 157 mg

$R_f$: 0.48 and 0.54 Eluent: $CH_2Cl_2$/MeOH 10:1

**Example 28: [N-(Ethoxycarboxymethyl)-N-(thymin-1-yl-acetyl)-2-aminoethyl]-2-cyanoethyl-(5'-(4-methoxytrityl-amino)-thymidine 3'-phosphate**

0.8 g (1.6 mmol) of the compound from Example 25 (precipitated from pentane and predried) is dissolved in 40 ml of dichloromethane and the solution is treated under argon with 1.2 mmol of bis(diisopropylammonium)-tetrazolide. After addition of 2 eq. of 2-cyanoethoxy-bis(diisopropylamino)-phosphine, the mixture is stirred at room temperature for 2 hours. The reaction mixture is partitioned between 40 ml in each case of dichloromethane and satd $NaHCO_3$ soln, the aqueous phase is extracted with dichloromethane a further three times and the combined organic phases are washed with NaCl soln and then dried over sodium sulphate. The oil resulting after evaporation of the solvent is dissolved in a little dichloromethane and the solution is added to 400 ml of pentane at 0°C. The solution is left at this temperature for a further 30 minutes and the precipitate is

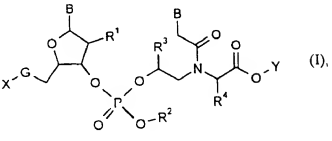
finally filtered off and dried. 629 mg of a white solid result, which in the TLC ($EA/CH_2Cl_2/NEt_3$ 45:45:10 (v/v/v)) shows two UV-absorbing points for the two diastereomeric phosphites. The crude product (200 mg; 0.64 mmol) is immediately further reacted with the compound from Example 20 analogously to Example 27. After chromatography on silica gel using $CH_2Cl_2$/MeOH gradients (70:1 to 30:1 (v/v)), the product is obtained in the form of a white solid.

Yield: 103 mg

$R_f$ 0.47 and 0.57 Eluent: $CH_2Cl_2$/MeOH 10:1

**Patent Claims**

1. Compounds of the general formula (I)



(I),

in which

$R^1$ represents hydrogen, hydroxyl, $C_1$-$C_{18}$-alkoxy, halogen, azido or amino,

$R^2$ represents a phosphate protective group customary in nucleotide chemistry, such as, for example, 2-cyanoethyl,

$R^3$ and $R^4$ independently of one another represent hydrogen, $C_1$-$C_4$-alkyl or together represent $C_1$-$C_4$-alkanediyl such as, for example, $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$ or $-C(CH_3)_2-$,

B represents all natural or unnatural nucleobases, such as, for example, thymine, uracil, cytosine, adenine, guanine, hypoxanthine or derivatives derived by chemical modification of these or halogenated precursors of these, optionally substituted on the amino groups by protective groups such as acetyl, trifluoroacetyl, trichloroacetyl, benzoyl, phenylacetyl, benzyloxycarbonyl (Z or Cbz), tert-butoxycarbonyl (Boc), allyloxycarbonyl, (9-fluorenyl)methoxycarbonyl (Fmoc) or other protective groups customary in peptide and nucleic acid chemistry,

G represents -NH- or -O-,

X represents hydrogen or any desired protective group known from peptide chemistry, such as, for example, Z, Fmoc or 4-methoxytrityl and

Y represents hydrogen, $C_1$-$C_6$-alkyl or any desired C-terminal protective group known from peptide chemistry, such as, for example, benzyl or tert-butyl.

2. Compounds of the general formula (I)

in which

$R^1$ represents hydrogen, hydroxy, $C_1$-$C_6$-alkoxy, fluorine, chlorine, bromine, azido or amino,

$R^2$ represents a phosphate protective group customary in nucleotide chemistry,

$R^3$ and $R^4$ independently of one another represent hydrogen, $C_1$-$C_4$-alkyl or together represent $C_1$-$C_4$-alkanediyl,

B represents all natural nucleobases, such as, for example, thymine, uracil, cytosine, adenine, guanine or hypoxanthine or halogenated precursors of these which are optionally substituted on the amino groups by protective groups such as acetyl, trifluoroacetyl, trichloroacetyl, benzoyl, phenylacetyl, benzyloxycarbonyl, tert-butoxycarbonyl, allyloxycarbonyl, (9-fluorenyl)methoxycarbonyl or other protective groups customary in peptide and nucleic acid chemistry,

G represents -NH- or -O-,

X represents hydrogen or any desired protective group known from peptide chemistry,

Y represents hydrogen, $C_1$-$C_4$-alkyl or any desired C-terminal protective group known from peptide chemistry.

3. Compounds of the general formula (I) according to Claim 1, in which

$R^1$ represents hydrogen, hydroxyl, methoxy, ethoxy, fluorine, chlorine, azido or amino,

$R^2$ represents 2-cyanoethyl,

$R^3$ and $R^4$ independently of one another represent hydrogen, methyl, ethyl, isopropyl or together represent $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$ or $-C(CH_3)_2-$,

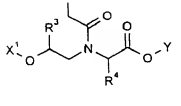
B represents all natural nucleobases, such as, for example, thymine, uracil, cytosine, adenine, guanine or hypoxanthine or halogenated precursors of these which are optionally substituted on the amino groups by protective groups such as acetyl, trifluoroacetyl, trichloroacetyl, benzoyl, phenylacetyl, benzyloxycarbonyl, tert-butoxycarbonyl, allyloxycarbonyl, (9-fluorenyl)methoxycarbonyl or other protective groups customary in peptide and nucleic acid chemistry,

G represents -NH- or -O-,

X represents hydrogen or any desired protective group known from peptide chemistry,

Y represents hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl or benzyl.

4. Compounds of the general formula (II)




(II),

in which

$R^3$, $R^4$ and B have the meanings indicated in the description of the compounds of the formula (I),

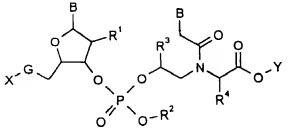
$X^1$ represents hydrogen or an acid-labile protective group known from peptide chemistry, such as, for example, silyl substituted by alkyl and/or phenyl, Z, Fmoc or 4-methoxytrityl, where in the case in which $R^3$ and $R^4$ simultaneously each represent hydrogen, optionally substituted alkoxycarbonyl and trityl are excluded and

Y represents $C_1$-$C_6$-alkyl or any desired C-terminal protective group known from peptide chemistry, such as, for example, benzyl or tert-butyl.

**Building blocks for DNA/PNA co-oligomers**

Abstract

The invention relates to compounds of the general formula (I)



(I),

in which the substituents have the meanings indicated in the description.

The compounds are suitable for the preparation of hitherto unknown strictly alternating PNA/DNA co-oligomers.